November 5, 2001

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Food and Drug Administration
Division of Dermatologic & Dental Drug Products, HFD-540
Center of Drug Evaluation and Research
Office of Drug Evaluation V
9201 Corporate Boulevard, 2nd Floor
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CONFIDENTIAL AND PROPRIETARY

Dear Dr. Wilkin:

Re: **NDA 18-662 – Accutane (isotretinoin) Capsules - S-044 System to Manage Accutane Related Teratogenicity (S.M.A.R.T.). Request for Meeting**

We refer to the approval of the above supplemental application on October 30, 2001 which provided for revisions to the labeling to reflect the System to Manage Accutane Related Teratogenicity (S.M.A.R.T.) Program, an enhanced risk management program with the public health goal of helping to prevent fetal exposure to Accutane.

As discussed with FDA during the review of the S.M.A.R.T. program, Roche has however, identified several areas of concern that will arise when multiple isotretinoin products are available on the marketplace with other S.M.A.R.T.- like programs. The attached document describes some of these concerns.

We would like to request a meeting with FDA to discuss issues relating to the potential public health consequences of having multiple isotretinoin products on the market. We want to work with FDA to assure that the public health goals we share are not compromised in a multi-product marketplace.

We propose the following objectives for such a discussion:

- To gain common understanding on the potential areas which could compromise 1) the viability and integrity of the S.M.A.R.T. program; and 2) its accompanying surveillance system when multiple isotretinion products become available.
- To discuss FDA-proposed solutions to the potential areas of concern that have been identified, thus maintaining the viability and integrity of the S.M.A.R.T program when other isotretinoin products come to market.
- To agree on intentions for specific responsibility and accountability of each manufacturer for their own program when multiple risk management programs become available.

Should you have any questions, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE INC.

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1. INTRODUCTION

Roche is committed to appropriate risk management to ensure the safe and effective use of Accutane. Roche has worked closely with FDA to develop and implement a comprehensive program that specifically addresses the area of pregnancy prevention. FDA and Roche have agreed no woman should start Accutane while being pregnant and that no woman should become pregnant while on Accutane. Roche believes that this pregnancy prevention program, including the assessment of such, as outlined in the Accutane Label Supplement Approval Letter (October 30, 2001), is an effective program for Accutane to meet these overall public health goals. Under the new program:

- a new yellow Accutane Qualification Sticker should be attached to the prescriber's regular prescription form to indicate the patient has been qualified to receive Accutane,
- all female patients must have two negative pregnancy tests as well as education about pregnancy before their first Accutane prescription,
- no Accutane prescriptions will be given for more than one month supply at a time and the patient must have a new negative pregnancy test before each new prescription,
- all female patients who are, or might become, sexually active with a male partner must use two forms of effective contraception simultaneously for at least one month prior to starting Accutane, during therapy, and for one month following discontinuation of the drug, and
- pharmacists will dispense Accutane only on receiving a prescription with the special Accutane sticker. Requests for refills without a new prescription and phoned-in prescriptions will not be filled.

Through the "System to Manage Accutane Related Teratogenicity" (S.M.A.R.T.) program, Roche has established a system to respond more quickly to these public health goals, while at the same time assuring high data standards and patient confidentiality. Furthermore, the Accutane pregnancy prevention risk management program will be assessed through a series of metrics, which are specific to key aspects of the S.M.A.R.T. program. FDA made clear in the October 30, 2001 Accutane Label Supplement Approval Letter that the S.M.A.R.T. program is a mandatory component of the Accutane Label.

Without full resolution of the issues addressed in this document, we are concerned about the ability of FDA, Roche, and other companies to maintain these high standards in a multiple isotretinoin product environment.

Roche's isotretinoin patent, as extended by pediatric exclusivity, expires on February 7, 2002. It is possible that isotretinoin products manufactured by other companies may be approved at that time. Roche assumes that the manufacturer of any isotretinoin product approved through an abbreviated new drug application (ANDA) will be required to implement a pregnancy prevention risk management program identical to the S.M.A.R.T.™ program in all material respects, in accordance with the statutory requirement that an ANDA drug bear labeling that is the same as that of the listed drug. We are concerned, however, that the simultaneous availability of multiple isotretinoin products supported by identical S.M.A.R.T.-like programs threatens to compromise the viability and integrity of any one of those programs. This has become increasingly clear to us as we have enhanced and refined the pregnancy prevention program that was already in place. Roche recognizes that this poses a challenge to FDA in carrying out its statutory mandate to protect the public health in an environment in which multiple isotretinoin products may be distributed by different manufacturers.

In brief, there is a fundamental implementation difficulty presented by state generic substitution laws. Assuming that the healthcare provider writes a prescription for Accutane, this generally will be substitutable at the pharmacy with any AB-rated isotretinoin product unless the healthcare provider requires that the brand be dispensed in accordance with state law. Thus, although the healthcare provider writes the prescription for Accutane (using yellow self-adhesive Accutane Qualification Sticker), obtains the necessary negative pregnancy tests, helps the female patient choose two safe and effective forms of contraception, obtains informed consent, seeks to enroll the patient in the Accutane Survey, and follows the other requirements of the pregnancy prevention risk management program, the healthcare provider will not have any way of knowing which manufacturer's product actually will be dispensed to and used by the patient (unless the prescriber prohibits substitution in accordance with states laws, which can vary from state to state). Furthermore, there is no way of knowing which surveillance program the female patient enrolls in, or if she enrolls in more than one. The issues multiply when consideration is given to the fact that subsequent prescriptions in the same course of therapy may be filled with products of different manufacturers, so there is no assurance of consistency for any single patient. This confusion will be further compounded by the fact that the S.M.A.R.T. process depends upon reliable metrics to guide the continual evaluation of this pregnancy prevention risk management strategy.

Roche has identified several areas of concern regarding the availability of multiple isotretinoin products, including: (1) public health surveillance, i.e., metrics; (2) healthcare provider and patient compliance with regard to which pregnancy prevention program they are participating in; and (3) reproducibility of Roche's current program of education, training and expertise. Therefore, we request to initiate a dialogue with the Agency to determine how FDA will ensure that the public health goals it shares with Roche are not compromised by the presence of multiple forms of isotretinoin. That is to say, how the program that Roche puts in place can be adequately tracked and measured in a real world situation and then potentially modified to meet the goal that no woman should start Accutane while being pregnant and no woman should become pregnant while on Accutane. Therefore, it is imperative that Roche has an accurate numerator and denominator in order to scientifically determine which components of the S.M.A.R.T. program are working appropriately and which need to be emphasized with the prescriber, pharmacist and / or patient. Roche is committed to working closely with FDA to identify issues relating to the public health consequences of having multiple isotretinoin products on the market.

2. PUBLIC HEALTH SURVEILLANCE

Roche's S.M.A.R.T. program contains several discrete requirements that must be fulfilled by the healthcare provider, pharmacist, and patient. The program is initiated with the healthcare provider joining S.M.A.R.T. by completing the Letter of Understanding, reading the Guide to Best Practices, and receiving yellow self-adhesive Accutane Qualification Stickers. He/she also may attend an optional Roche-sponsored CME/CEU that specifically addresses the risks associated with Accutane therapy and the proper use and prescribing of the product in order to reduce or eliminate these risks. The healthcare provider then confirms that the female patient of childbearing potential has been qualified to receive a prescription for Accutane through assurance of negative pregnancy test(s); provides appropriate counseling to her on the choice and use of two forms of safe and effective contraception; encourages her to register in the Accutane Survey (Slone); and ensures that she reads, understands, and signs the Accutane Patient Information/Informed Consent. When the female patient appears at the pharmacy with her Accutane prescription, the pharmacist will only fill an Accutane prescription if the yellow self-

adhesive Qualification Sticker is affixed, dispense no more than a one-month supply, and dispense the product with an Accutane Medication Guide. This entire process is repeated for each of the patient's Accutane prescriptions throughout the course of her therapy (see Appendix 1). Clearly, all parties in this prescribing chain share responsibility for the safe and effective use of Accutane.

To construct a balanced and reliable assessment of this comprehensive and multi-faceted pregnancy prevention risk management program, Roche has developed a system to obtain relevant information from all constituent stakeholders. This comprehensive program evaluation system consists of the longitudinal Accutane Survey (Slone), the point-in-time DMD pharmacy audit, and a 3rd metric (to be agreed upon between Roche and FDA). With multiple isotretinoin products on the market, the risk of confounding both the numerator and denominator of each of these metrics is high. For example, substitution at the pharmacy level will make it impossible to determine the average length of therapy. As no refills are allowed with isotretinoin, if a female patient starts her course of therapy on Accutane but completes her course of therapy on another manufacturer's product, she will be counted as a new patient start for both Accutane and the other manufacturer's product. Therefore, her course of therapy will be one month for Accutane and n-1 months for the other manufacturer's product. Switching at the pharmacy level presents the most significant issue to the integrity of the risk management program. IMS-Health data, for example, has shown that so far in 2001, 74% of all prescriptions written for Klonopin are filled with another manufacturer's product.

As FDA is fully aware, no isotretinoin pregnancy prevention risk management program can be adequately assessed unless each manufacturer has as accurate assessment of the number of female patients on its product, the number of female patients enrolled in its program, and the characteristics of their female patients. Inaccurate counting is likely to result if a prescription is substituted at the pharmacy level. Scenarios might arise where the metrics could be artificially exceeded or unmet depending on who is considered part of the numerator and who is considered part of the denominator. For example:

- If a female patient signs up for the Accutane S.M.A.R.T. program, receives a prescription for Accutane, and fills the prescription for Accutane, her data will be correctly counted in both the Accutane numerator and denominator.

- If a female patient signs up for the Accutane S.M.A.R.T. program, receives a prescription for Accutane, and has it substituted at the pharmacy for another manufacturer's product, her data will be incorrectly counted in the Accutane numerator, correctly excluded from the Accutane denominator, correctly counted in the other manufacturer's product's denominator and incorrectly excluded from the other manufacturer's numerator.

- If a female patient signs up for the Accutane S.M.A.R.T. program, receives a prescription for Accutane, and has her first prescription filled as Accutane and her subsequent prescriptions filled with another manufacturer's products, her data will be correctly counted in the Accutane numerator (and potentially in the other manufacturer's product's numerator) and incorrectly counted in both the Accutane and another manufacturer's product's denominator.

The above examples provide just a few of many possible scenarios. The numerator could be further confounded if the female patient registers for more than one pregnancy prevention program during the same course of treatment.

2.1 Potential for Pharmacy Substitution

Given the potential to confound each manufacturer's numerator and denominator, options must be explored to minimize confusion and / or prevent switching at the pharmacy level. One way to partially mitigate this situation would be placing a mandatory "dispense as written" or "brand medically necessary" on each of the yellow self-adhesive Accutane Qualification Stickers. However, due to mandatory substitution laws and formulary restrictions, this will not completely solve the problem.

3. HEALTHCARE PROVIDER AND PATIENT COMPLIANCE

The S.M.A.R.T. program was designed during a period with only one isotretinoin product on the market, i.e. Accutane. Consequently, there could be potential for confusion when other isotretinoin product(s) enter the market. This confusion could potentially affect both the healthcare provider and the patient.

The yellow self-adhesive Accutane Qualification Sticker is critical documentation linking an Accutane prescription to two negative pregnancy tests, the use of two safe and effective forms of contraception, understanding and signing the Accutane Patient Information/Informed Consent, and offering enrollment in the Accutane Survey (Slone). This linkage is an important risk management step, in addition to the other steps necessary to qualify a patient to receive a prescription for Accutane. If a female patient is familiar with one qualification sticker and receives another, she may be unsure of which product she is taking and may, in her confusion, enroll in and complete a survey for a product she was not prescribed or may complete more than one manufacturer's survey. Questions relating to the correct linkage of adverse events with a particular manufacture's products also are raised. While the issue of appropriate reporting arises in other multiple-manufacturer scenarios, it rarely is of any regulatory significance because most times it can be corrected through a labeling modification, which all versions of the product would carry. In the case of isotretinoin, however, accurate reporting is critical in determining the success or failure of each manufacturer's individual pregnancy prevention risk management program, which ultimately relates to the overall public health goals.

Additionally, multiple isotretinoin products will presumably require healthcare providers to have more than one isotretinoin pregnancy prevention risk management program available in their office. There may be confusion as to which manufacturer's program to use, which contraceptive counseling line to call, or which manufacturer to query should a medical question or safety concern arise. Again, the healthcare provider could use the S.M.A.R.T. program and enroll his/her female patients in this program, only to have the Accutane prescription substituted at the pharmacy level. In this scenario, the healthcare provider would be unaware of which product their female patient is actually taking throughout the course of her therapy. If experience is a guide, virtually all of the spontaneous adverse event reports will come into Roche. Therefore, there will have to be a mechanism in place that will ensure that these cases are correctly linked to the appropriate isotretinoin manufacturer without placing an undue burden on Roche.

4. EDUCATION, TRAINING, AND ROCHE EXPERTISE

Part of Roche's comprehensive pregnancy prevention risk management program includes a multi-faceted program for educating and training healthcare providers regarding the risks associated with Accutane therapy and the proper use and prescribing of the product in order to reduce or eliminate these risks. These educational services provided by Roche are exclusively focused on

and created through our understanding of Accutane and the programs associated with Roche's isotretinoin product.

Roche has had many years of experience providing educational support to healthcare providers and patients through its scientifically trained field force and marketing department. As the S.M.A.R.T. program is rolled-out, Roche foresees an even greater need for medical education. Roche will provide healthcare providers with the "S.M.A.R.T. Guide to Best Practices" which was specifically designed to aid their proper use of Accutane.

If there are multiple isotretinoin products on the market, each with pregnancy prevention risk management materials and approaches to program support, healthcare providers will have the responsibility of assuring that their patients receive the correct information about the product and program prescribed and dispensed. Roche currently has trained Sales Specialists who will be providing instruction and guidance to healthcare providers regarding roll-out of the S.M.A.R.T. program, which is one of the key elements to encouraging and helping healthcare providers to make a smooth transition into joining and utilizing the S.M.A.R.T. program. Training brochures and educational materials for healthcare providers are also planned to assist the field force efforts.

Also critical to ensuring the success of S.M.A.R.T. is the roll-out of the program to the 56,000 pharmacies in the U.S. Again, Roche professionals will be key in training pharmacists and answering their questions, as well as providing training brochures and educational materials. These Roche professionals are a critical element to ensuring the smooth integration between pharmacists and healthcare providers and patients.

Working in concert with the FDA, Roche has developed and implemented training specifically designed for the Roche S.M.A.R.T. program. Roche has been providing voluntary CME/CEU programs to healthcare providers (physicians/nurses) to train them in pregnancy prevention and contraception. Many healthcare providers have benefited from this training, advancing the public health goals.

Additionally, any health care professional can contact the Roche Professional Service Center where an Accutane Pregnancy Safety Specialist will be available to help answer his/her questions regarding Accutane and pregnancy. These Specialists are trained Registered Nurse with several years' experience in both clinical practice and work in the Department of Drug Safety and Risk Management. These Specialists and the associated counseling services they provide have been in place for well over 15 years. Depending upon the nature of the question, or concern the health care professional poses, they assist healthcare providers with all available resources regardless of exposure status of the pregnancy concerned. This may include literature searches, literature references, product information, and aggregate data from 20 years worldwide Accutane pregnancy safety experience.

In addition, the Specialists take a full patient history and help provide data which can assist the healthcare provider in assessing their patient's pregnancy risk. Extensive follow-up is also provided in the event the healthcare provider may require additional information, or if another specialist, involved in patient care could benefit from discussion with the Roche Specialist.

Roche is committed to continuing to provide these services to healthcare providers and patients but only when Accutane is dispensed.

4.1 Additional Educational Aspects of the S.M.A.R.T. Program

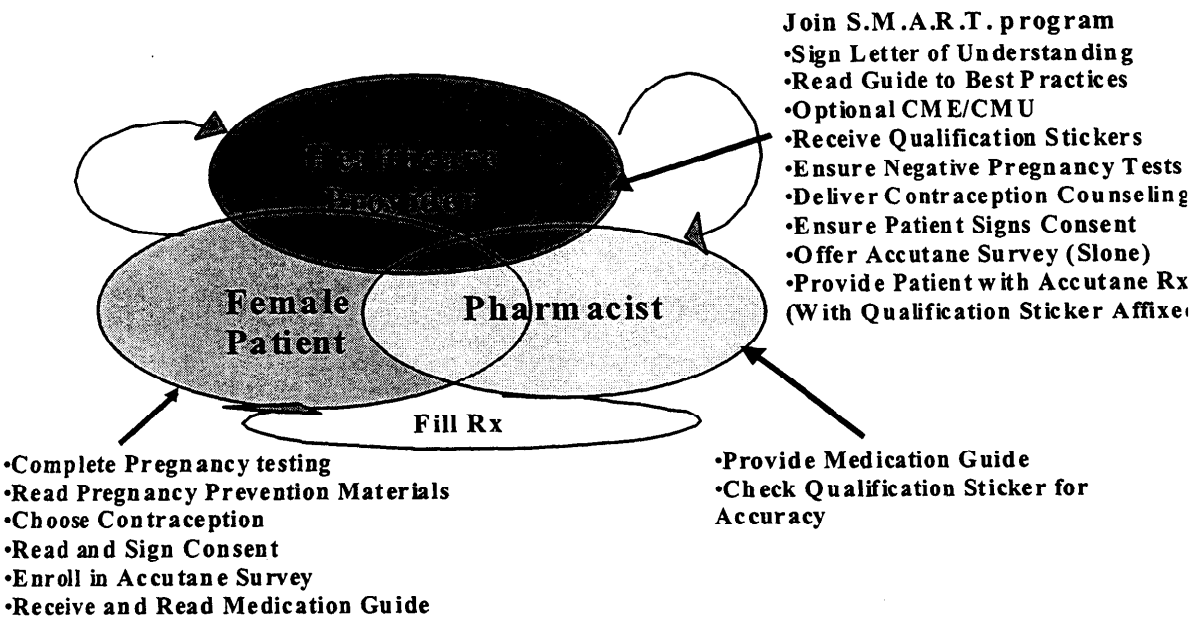
Roche provides an 800 number for patients to call with questions and/or concerns regarding contraception and pregnancy. The Roche Specialist continues to follow-up with the healthcare provider throughout the pregnancy course, through delivery, and throughout the first two years of the child's life. Finally, Roche also provides free contraceptive counseling to patients as listed in the Patient Information/Consent that is part of the Accutane package insert. The safety of patients using Accutane is our primary concern, and Roche will bear the full costs of either the Roche Specialist or the free contraceptive counseling and referrals, but only for prescriptions actually filled with Accutane.

4.2 Free Pregnancy Tests

Roche provides free pregnancy tests as part of the current pregnancy prevention risk management program for female Accutane patients for the initial, second, and monthly pregnancy testing during Accutane therapy. This offering is spelled out in the black box section of the Accutane package insert. This is done in order to facilitate obtaining the two negative pregnancy tests from potential female Accutane patients before the initial prescription of Accutane is written. Here as well, each manufacturer should bear the cost of pregnancy tests only for patients actually using their product.

5. CONCLUSION

For all of the reasons outlined in this document, Roche believes that it is essential to initiate discussions with FDA regarding the specifics as to how the Accutane pregnancy prevention risk management requirements will be applied to other manufacturers of isotretinoin products and how the S.M.A.R.T. and other pregnancy prevention risk management programs will be implemented and measured in a multiple-product environment to ensure the integrity of Roche's program.



Appendix 1: Accutane Pregnancy Prevention Risk Management Program